



# ATTACHMENT 3



## **I. Qualifications**

### **ADMINISTRATIVE RECORD**

I am Suresh H. Moolgavkar, a physician with a Ph.D. in mathematics and post-doctoral training in Epidemiology and Biostatistics.

I am currently a Full Member of the Fred Hutchinson Cancer Research Center and Professor of Epidemiology and Adjunct Professor of Biostatistics at the University of Washington in Seattle. I have served on the faculties of the Johns Hopkins University, Indiana University, the Fox Chase Cancer Center and the University of Pennsylvania. I have been a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, the International Agency for Research on Cancer in Lyon, and the German Cancer Research Center in Heidelberg. I have served on numerous review panels and as a consultant to the National Cancer Institute, the Environmental Protection Agency, Health and Welfare, Canada, The International Agency for Research on Cancer, and the Chemical Industry Institute of Toxicology, among others. I am the author or co-author of more than 130 papers in the areas of Epidemiology, Biostatistics, and Quantitative Risk Assessment, and have edited three books in these areas. I have served on the editorial board of 'Genetic Epidemiology' and am currently one of the editors of 'Risk Analysis – An International Journal'. I am an elected member of the American Epidemiological Society. I was given the Founders Award by the CIIT Centers for Health Research in 1990 and the Distinguished Achievement Award by the Society for Risk Analysis in 2001.

I have published several papers on fiber-induced carcinogenesis within the last half dozen years.

My curriculum vitae is attached as Exhibit A to this report. The list of publications I have authored in the last ten years is included in my curriculum vitae. I have not testified as an expert at trial or deposition in the past four years.

I am being compensated for this report at an hourly rate of \$250. Payment is not contingent on a specific outcome. I reserve the right to supplement or revise this report to reflect my review of new information, as appropriate.

In preparing this report, I have considered my knowledge as a physician with a Ph.D. in mathematics and post-doctoral training in Epidemiology and Biostatistics as well as the material listed in the References section herein and other material provided to me by Holme Roberts & Owen.

## **II. Executive Summary**

I have reviewed the literature on the health impacts of asbestos exposure in the Libby area. In addition to the occupational cohort studies conducted by Amandus and colleagues and by McDonald and colleagues I have reviewed the studies conducted by the Agency for Toxic Substances and Disease Registry. I have also reviewed a draft manuscript by Dr. Alan Whitehouse. In my expert opinion there is absolutely no evidence that the Libby fibers are any more toxic than other amphiboles. In particular, for cancer (lung cancer and mesothelioma) a critical examination of occupational cohort studies strongly suggests that the Libby fibers are no more toxic than those considered in the EPA IRIS file for asbestos. While there is no IRIS potency number for the non-cancer end points, particularly non-malignant respiratory disease, there is no evidence to suggest that the Libby fibers are any more toxic than other asbestos fibers. Most importantly all studies dealt with individuals who had been exposed to asbestos in Libby before the closure of mining operations in 1990. Many of these individuals were occupationally exposed to high levels of asbestos. None of the studies has any direct information on the impact of exposures post-1990, much less of current exposure, on the health of residents of Libby.

### **III. Fiber-Induced Disease**

There is incontrovertible evidence that prolonged exposure to either natural or man-made fibers is associated with increased incidence of lung cancer, mesothelioma and non-malignant respiratory disease. While the epidemiological evidence is strongest for asbestos, there is considerable experimental evidence that all fibers have the same potential to cause disease. Biopersistence is the term used to describe the longevity of fibers in tissues, which is determined by the rate at which the fibers are cleared by biological defense systems. The mechanisms of fiber-induced disease are not well understood but there appears to be broad consensus that the biopersistent long thin fibers are the most toxic (see Moolgavkar et al, 2001, for a brief review).

The importance of fiber length and biopersistence is recognized by regulatory agencies, such as the European Commission (EC). In 1997 the EC issued a directive regarding the labeling of fibers as potential carcinogenic hazards. Fibers could be exempted from the requirement to be labeled as carcinogens if testing in animals by inhalation showed that fibers longer than 20 microns had a weighted half-life of less than 10 days. Thus all long thin fibers have the potential to cause disease. Long thin fibers of amphibole asbestos are among the more toxic fibers because they are cleared only slowly from tissues, i.e., they are highly biopersistent. Prolonged exposure to high concentrations of such fibers, whether occupational or environmental, can lead to malignant and non-malignant disease.

The United States Environmental Protection Agency (EPA) has posted an Inhalation Unit Risk number for asbestos in its Integrated Risk Information System (IRIS), which is the agency's best estimate of the life-time carcinogenic potency of asbestos for continuous exposure to 1 fiber/ml from birth. One of the allegations that the Denver regional office of EPA appears to make is that the Libby fibers are particularly potent and that risks posed by these fibers are higher than would be estimated by application of the Unit Risk (UR) in IRIS. I have examined the available data, including the published epidemiological studies (Amandus et al, 1986; McDonald et al, 1986; McDonald et al,

2002) and find no evidence that the Libby fibers are any more potent than other amphiboles. I discuss this in detail below.

The other issue of importance is the contribution made by exposures after 1990, when the mining operation was shut down, to the burden of asbestos-related disease and lung impairment in Libby. The level of environmental exposure to Libby tremolite after the shutting down of mining operations is being addressed in the expert reports of Drs. Anderson and Lee. I have examined the studies conducted by the Agency for Toxic Substances and Dose Registry (ATSDR), and Dr. Whitehouse and it is my opinion that these studies cannot address this issue. All individuals enrolled in these studies were exposed prior to 1990 and, given the long latent period of asbestos-related disease, it is impossible to say what contribution, if any, exposure post-1990 made to their reported disease or impairment. This issue is also discussed in detail below.

#### **IV. EPA's Unit Risk for Asbestos Carcinogenesis**

In 1986, the U. S. Environmental Protection Agency (EPA) published a report, Airborne Asbestos Health Assessment Update (EPA 1986), which critically evaluated the scientific asbestos literature available at that time. Among other things, the report estimated the fractional increased risk of lung cancer and mesothelioma per unit exposure of asbestos. The bases for the lung cancer potency estimate were 10 epidemiological studies of workers in the textile production, friction products manufacturing, insulation production, and mixed product manufacturing or use industries. The bases for the mesothelioma potency estimate were 4 of those studies for which sufficient data existed to allow for the estimation of duration and intensity of asbestos exposure, adjusted by the results of several of the other studies. The report calculated risk by life table methods using a relative risk model for lung cancer and an absolute risk model for mesothelioma.

In 1993, EPA published an Integrated Risk Information system (IRIS) profile (EPA 1993) on asbestos, which provided an estimate of the inhalation unit risk of 0.23 per (f/ml). This value can be interpreted as follows. A cohort of 100,000 individuals exposed

continuously to a constant concentration of 1 fiber/ml of asbestos from birth would experience 23,000 extra lung cancer or mesothelioma deaths due to the exposure. The 1986 EPA report dealt with occupational exposure to asbestos. In order to derive the value in the IRIS profile the EPA adjusted for the quantity of fiber that a person could be expected to inhale under environmental conditions. Because the unit risk value was based on fiber counts made by phase contrast microscopy (PCM), the IRIS profile warns against applying it directly to measurements made by other analytical techniques, such as electron microscopy. Since PCM detects only fibers longer than 5 microns in length and wider than 0.4 microns in width, this puts a practical lower limit upon the dimensions of fibers that will be included in a risk calculation using the EPA potency figure. The IRIS profile also states that PCM measurements made in conditions where fibers other than asbestos are present may not be reliable.

It is important to bear in mind that, as described above, the EPA unit potency value of 0.23 per (f/ml) was derived from a number of epidemiology studies that spanned diverse industries where different types of asbestos fibers were used. Furthermore, the dimensional characteristics of the fibers were not taken explicitly into consideration in deriving the potency value. At best, this figure should be considered as being representative of asbestos toxicity in the large and not reflective of the unique characteristics of a specific type of asbestos fiber.

## **V. Occupational Cohort Studies of Libby Fibers and Cancer Mortality**

Additional studies have been published that provide information about the risk to humans who inhale Libby fibers. In the following paragraphs we review these studies with an eye to developing a unit potency value that reflects the specific characteristics of Libby fibers.

### The Amandus Studies

In 1982, the National Institute of Occupational Safety and Health initiated studies of the environmental exposures, and mortality and morbidity of employees who were employed at the Libby, Montana site. In 1987, Amandus et al. published three papers (Amandus et al a, b ,c) dealing with various aspects of this investigation. The first paper dealt with estimating the time-weighted average (TWA) fiber exposure for each job in the Libby facility and characterizing the type and dimension of fibers in the vermiculite. The third paper estimated the exposure-response relationship for radiographic findings from estimates of cumulative exposure. It is the second paper, (Amandus et al. 1987b) in which the exposure-response association between cumulative exposure and mortality was estimated, to which I turn my attention.

Amandus et al. studied a cohort of 575 men hired prior to 1970 and employed at least 1 year at the Libby site. Death certificates were obtained for 159 of the 161 men in this cohort who died, from which the underlying cause of death was coded. Using estimates of the TWA fiber exposure for each job (Amandus et al. 1987b), the authors developed for each person in the cohort an estimate of cumulative exposure.

Man-years at risk of dying were accumulated from date of hire to December 31, 1981 or to date of death for those who died before that date. In this manner, the cohort contributed 13,502 man-years of follow-up. Using U.S. deaths rates as the standard, Standardized Mortality Ratios (SMRs) were computed and tests for statistical significance employed to determine whether the SMRs were significantly different from 100. The authors found that the SMR was significantly increased for lung cancer (SMR = 223) and nonmalignant respiratory disease (NMRD) (SMR = 243) but not for other selected causes of death. For reference, an SMR of 100 would indicate no increase in disease. Thus the analyses in Amandus et al indicated that the risk of lung cancer was increased 2.23 fold and that of NMRD 2.43 fold over the general US population. The SMRs for various cumulative exposure categories (<50, 50-99, 100-399, and >399 f/ml.yrs) showed elevated levels for lung cancer and NMRD, but statistical significance was achieved only at the >399

f/ml.yrs cumulative exposure for lung cancer and the <50 and >399 f/ml.yrs cumulative exposure level for NMRD.

A non-threshold linear regression model was fitted to the SMRs for lung cancer in each of the four exposure categories described above. The authors found that the slope of the regression line (potency) for the subset of the cohort consisting of workers with over 20 years of latency was 0.0058. Note that the figures quoted here are one-hundredth of the ones given in the paper to make them consistent with the way potencies are used in the IRIS document. That is every f/ml.yr increase in exposure leads to a 0.58 % increase in lung cancer risk. In tables below I show how this risk and risks estimated from the McDonald studies (see below) translate into unit risks (URs) for asbestos as defined in IRIS. The URs thus obtained provide a direct comparison of the potency of the Libby fibers with the potency of the fibers used to derive the UR in IRIS.

#### The McDonald Studies

A complementary line of research to the NIOSH investigations was undertaken by McDonald et al., at the invitation of WR Grace, to assess the health effects of working in the Libby vermiculite mine. The results were reported in four publications dealing respectively with a cohort mortality study, a cross sectional radiographic survey, an investigation of asbestos bodies in sputum, and an electron microscopic analysis of lung tissue samples at necropsy from ex-employees. The first of these studies, the cohort mortality study (McDonald et al, 1986), is most relevant to the question of deriving of a UR value for Libby fibers. A fifth study (McDonald et al, 2002) reporting further follow-up of the mortality cohort has recently appeared and will also be discussed.

The cohort study consisted of all male workers who were employed at Libby before January 1, 1963 for a period of at least 1 year. Of the 406 men who met these criteria, 226 were alive on July 1, 1983 and 165 reported dead. Another 14 men were known to be living on December 31, 1981 but their subsequent status was unknown. The cause of death was coded from death certificates obtained for 163 of the 165 men who died.

Exposure estimates were made, as in the Amandus et al. studies, by estimating prevailing fiber concentrations at work locations and, through work histories, the cumulative exposure of each individual in the cohort.

SMRs were computed by comparing mortality of the total cohort with that of white men in the United States and Montana death rates. The authors found a substantial excess number of deaths from respiratory cancer (SMR = 245) and from NMRD (SMR = 255). Using Montana death rates instead of U. S. national death rates increased the SMR for respiratory cancer to 303. A non-threshold linear regression model was fitted to the SMRs for respiratory cancer in four exposure categories among the subcohort of workers with at least 20 years of latency. The estimate of the slope of the regression line (potency) was reported to be 0.013, which is quite a bit higher than that reported by Amandus. I have rerun the regression analyses on the data presented in McDonald et al and am unable to reproduce this result. The results of my analyses are presented below in table 1.

Although there is considerable overlap in the cohorts considered by Amandus and McDonald, the results of analyses are somewhat different with McDonald reporting a substantially larger regression coefficient. McDonald et al. attribute these differences to (1) different although overlapping cohorts; (2) criteria for inclusion in the cohorts; (3) interpretation of the exposure data; and (4) coding of the death certificates. There could be other reasons as well for these differences. For SMR computations, McDonald et al. used Montana death rates as the standard, whereas Amandus et al. used the U.S. death rates. Furthermore, the exposure categories considered by the two groups of investigators were different. Finally, while Amandus et al used lung cancer (ICD codes 162 and 163) for their SMR analyses, McDonald et al used respiratory cancer (ICD codes 160-163).

In a recently published paper, McDonald et al (2002) extended their analyses to mortality in the cohort through 1999. The SMR for respiratory cancers with the extended follow-up was reported to be 240, which is virtually identical to that reported in the earlier

publication. No regression analyses were reported in this paper. However, I present some results of my own analyses below.

## **VI. Regression Analyses of the McDonald Studies**

I note that in the Amandus et al and McDonald et al studies the linear regression analysis was performed on a subset of the original cohort, consisting of workers with 20 or more years of latency. Such regression analyses could be performed on the entire cohort as well, but are not reported in those papers. While the Amandus et al paper reports SMRs for lung cancer in four broad exposure groups, it does not report the average exposures in each of these groups, which are required for regression analyses. Thus I could not run any new regression analyses on the data in Amandus et al. The requisite information is provided in the McDonald et al paper, however, and I ran a number of regression analyses on the SMRs for respiratory cancer on the data presented in that paper on both the full cohort and on the subcohort of individuals with latency greater than 20 years. I then used the results of these analyses to compute the associated Unit Risks (URs). The computed URs indicate that the Libby fibers are no more toxic than the fibers that went into the computation of the EPA UR of 0.23.

Since smoking is a strong risk factor for lung cancer with which asbestos interacts multiplicatively, it is important, if possible, to adjust for smoking when examining the association between asbestos and lung cancer. The prevalence of smoking was extremely high in the Libby occupational cohort. Amandus et al report that approximately 80% of the workers were smokers, and states that the risks estimates for asbestos may be biased upwards because of this fact. Using the estimate mentioned in Amandus et al of prevalence of smoking in the general male population of 67%, I used a crude procedure suggested by Amandus et al (1987a) to adjust the SMRs in McDonald et al and performed regression analyses on these adjusted SMRs as well. The estimated lung cancer potencies (slopes of the regression lines) for adjusted and smoking-adjusted SMRs are shown in table 1 below. The potency used by the EPA and the potency from the Amandus et al paper are also included for comparison. We note that all estimated

potencies in the Amandus and McDonald cohorts are less than 0.01, the potency in the EPA 1986 document, which was used in IRIS to develop the UR. It follows that the UR for the Libby fibers will, of necessity, be less than the UR of 0.23 presented in IRIS. The computed URs are shown in table 3.

Table 1: Potencies (regression slopes,  $K_L$ ) for lung cancer from EPA, the Amandus subcohort with latency greater than 20 years, the entire McDonald cohort and the subcohort with latency greater than 20 years. NA = not adjusted for smoking; A = adjusted for smoking.

EPA (1986)	McDonald et al. (1986)				McDonald et al. (2002)		Amandus et al. (1987)	
	Entire cohort		Sub-cohort		Sub-cohort		Sub-cohort	
	NA	A	NA	A	NA	A	NA	A
0.01	0.0075	0.0058	0.0096	0.0075	0.0056	0.043	0.0058	*

\* Could not be calculated from data in paper.

## VII. Development of Unit Risk Values for Libby Fibers

I will use the procedure followed in IRIS to compute the Unit Risks associated with the various potencies for lung cancer ( $K_L$ ) presented in table 1. The EPA develops a Unit Risk for cancer in the following steps.

1. Estimate potency for lung cancer ( $K_L$ ) from the totality of available occupational cohort studies. The EPA estimates that  $K_L = 0.01$ .
2. Estimate potency for mesothelioma ( $K_M$ ) from the occupational cohort studies. The EPA estimates that  $K = 10^{-8}$ . The background rate of mesothelioma is assumed to be 0, and the incidence of mesothelioma in exposed populations is assumed to increase as a cubic with a latency of 10 years.
3. Adjust these potency numbers to account for the different amounts of air inhaled by a person occupationally exposed (10 cu m per 8-hour day, or 50 cu m per week) and a person environmentally exposed (20 cu m per 24-hour day, or 140 cu m per week). The adjustment factor is thus 2.8 (140/50).

4. Use these adjusted estimates of  $K_L$  and  $K_M$  along with life tables for male and female mortality to estimate the excess (over background) risks of lung cancer and mesothelioma in male and female populations for continuous exposure from birth to 1 fiber/ml.
5. A weighted average of total cancer excess risks in males and females is an estimate of the Unit Risk.

The EPA procedure results in the following table, which is adapted from table 6-3 in EPA (1986).

Table 2: Lifetime excess risk per (fiber/ml), also known as Unit Risk.

	Male	Female	<b>Combined</b> (weighted average)
Mesothelioma risk	0.129	0.184	<b>0.157</b>
Lung cancer risk	0.114	0.035	<b>0.074</b>
Total risk	0.242	0.219	<b>0.230</b>

Adapted from EPA 1986

$K_L = 2.8 \times 0.01$ ;  $K_M = 2.8 \times 10^{-8}$

Columns may not add up because of roundoff

I used the same procedure to estimate Unit Risks associated with the range of potencies for lung cancer ( $K_L$ ) presented in table 1. Because neither Amandus et al. nor McDonald et al. derived mesothelioma rates, this table maintains the mesothelioma rates used by EPA in its derivation of the IRIS Unit Risk value. However, it is reasonable to assume that  $K_M$ , the mesothelioma constant, would change by the same multiple as  $K_L$ , the lung cancer potency (i.e.,  $K_L/K_M$  would remain constant over the different studies). In fact, EPA in its 1986 analysis derived a common value for this ratio that it used to derive the mesothelioma unit potency factor. The resulting Unit Risks are shown in table 3 (combining sex). The table shows the effect both of using the EPA mesothelioma potency and of adjusting the mesothelioma potency so that the ratio  $K_L/K_M$  is constant. Since I was not able to recalculate linear regression figures from the Amandus et al. study, only the effect of adjusting for mesothelioma is shown for that study.

The multiplicity of estimates of Unit Risk shown in table 3 may appear confusing at first glance. The range of numbers is meant to show, however, that many different ways of calculating Unit Risk all yield numbers that are less than the Unit Risk in IRIS. The highest Unit Risks in table 3 are obtained with no adjustment for smoking and no adjustment for mesothelioma potency. These estimates almost certainly over-estimate the Unit Risk. Note that adjustment for smoking means that the potency for lung cancer has been adjusted to account for the fact that the Libby occupational cohort contained a much higher proportion of smokers than the general population from which the control rates were drawn for computation of SMRs. Not adjusting for this difference in smoking habits results in an upward bias of the lung cancer potency of Libby asbestos and, as a consequence, an upward bias in the Unit Risk. The one lesson to be taken away from table 3 is that even under the most conservative assumptions the Unit Risk for Libby fibers is no higher than the Unit Risk presented in IRIS.

Table 3: Summary of Unit Risks derived from the potencies in table 1. NMA (no mesothelioma adjustment): Unit Risk calculated using the potency value for mesothelioma given by EPA; MA (mesothelioma adjusted): Unit Risk calculated by adjusting the mesothelioma potency as described in the text

	McDonald et al. (1986)				McDonald et al. (2002)		Amandus et al. (1987)	
	Entire cohort		Sub-cohort (>20 yr exp)		Sub-cohort (>20 yr exp)		Sub-cohort (>20 yr exp)	
	NMA	MA	NMA	MA	NMA	MA	NMA	MA
Adjusted for smoking	0.199	0.134	0.212	0.173	0.188	0.099	*	*
Not adjusted for smoking	0.212	0.173	0.227	0.221	0.198	0.129	0.199	0.136

\* could not be calculated with data published in paper

### **VIII. Conclusions Regarding Cancer Potency of Libby Fibers**

I conclude that the Amandus et al. and the reanalyzed McDonald et al. studies produce risks that are similar to, but generally lower than, the EPA Unit Risk value reported in IRIS. The range from lowest to highest Unit Risk values is about 2, which is not unexpected in view of the large uncertainties involved in any analyses of this type. These data strongly indicate that Libby fibers are not any more toxic than the fibers considered by EPA in developing its IRIS Unit Risk value. To the contrary, the data suggest that the Libby fibers could have a Unit Risk less than one-half of the value given in IRIS. Moreover, these computations are conservative. There is clear indication in both the Amandus and the McDonald data that the exposure-response relationship for SMRs is non-linear, suggesting that the risks at lower, environmental, levels is less than would be inferred from the linear regression. The non-linearity of an exposure-response relationship for lung cancer SMRs is supported by a recent comprehensive and critical review of the epidemiological studies of asbestos and lung cancer (Hodgson and Darnton, 2000).

## **IX. The Agency for Toxic Substances and Disease Registry (ATSDR) Studies**

In response to concerns about asbestos exposure and its health consequences the ATSDR undertook two studies in the Libby area in the late 1990s. One was a mortality study, which used standard epidemiological procedures to investigate whether mortality from specific causes known to be associated with asbestos exposure was elevated in the Libby area. The second was a radiographic study of over 6,000 current or former residents of the Libby area. While historical exposures to asbestos, before the closing of mining operations in 1990, were high the crucial issue here is if, and to what extent, exposures post-1990 contributed to the burden of asbestos-related disease in Libby. The ATSDR studies cannot address this issue as I discuss in more detail below.

### The ATSDR Mortality Study

The ATSDR undertook a study of mortality from specific causes in the Libby area over the 20-year period 1978-1998. Numbers of deaths from specific causes were compared with numbers that would be expected under national and Montana death rates. Standard epidemiological and statistical techniques were used to compute SMRs and their confidence intervals. Given the asbestos exposure in this population the main cancers of interest were lung cancer and mesothelioma.

The ATSDR reports a small non-significant increase in lung cancer deaths within Libby City and the extended Libby area using Montana death rates as the standard. With US death rates as the standard, no increase in lung cancer deaths is reported. This finding is surprising in view of the fact that SMRs were significantly increased in the occupational cohorts studied by Amandus and McDonald, and suggests that lung cancer may actually be decreased in residents of Libby who did not work at the mine. In any case, the number of lung cancer deaths over the period of the study offers no evidence that environmental exposures either pre- or post-1990 contributed to the lung cancer mortality in the area.

The ATSDR reports four cases of mesothelioma over the period of the study. Since the background rate of mesothelioma is close to zero, this number points to a significant elevation of risk in the Libby area. However, four cases of mesothelioma are identified in the McDonald occupational cohort, and it seems highly likely that these are the cases identified by ATSDR. Thus, the cases in ATSDR can, in all likelihood, be explained on the basis of occupational exposure. As in the case of lung cancer, this study offers no evidence that environmental exposure either pre- or post-1990 contributed to mesothelioma deaths in the Libby area.

I am aware that a number of additional cases of mesothelioma have been reported beyond those found in the ATSDR or McDonald (1986) studies. I have reviewed Attachment 38 to EPA's letter of June 4, 2002 that provides the names of 19 people (there is some ambiguity about the exact count) who reportedly have mesothelioma. Of this number, six are listed as "not a worker," which I assume means that they were not occupationally exposed. However, no further information is given about the conditions of their exposure. McDonald (2002) reports 8 additional cases of mesothelioma deaths since July 1983 bringing his total to 12 workers, cases that were likely cited in Attachment 38. In any case, these findings do not shed any additional light on whether post-1990 exposure contributed to mesothelioma deaths in the Libby area.

Among the causes of death other than cancer, of most interest are the non-malignant respiratory diseases (NMRD), particularly asbestosis. Eleven deaths from pneumoconioses are reported over the period of the study. All of these are labeled asbestosis in the ATSDR report, although it is not clear how this diagnosis was verified. In any case, the SMR is reported to range between 36 and 47 (depending on the geographic area of analysis) using the Montana rates as the standard, and between 60 and 75 using the US rates as the standard. Clearly the Montana rates are the appropriate rates to use for this population. Nonetheless, it is clear that deaths from asbestosis are significantly elevated. Of note, however, is the fact that 10 of the 11 deaths were among males suggesting strongly that occupational exposures were involved in these deaths.

There is little evidence that environmental exposures were involved in the deaths from asbestosis.

In conclusion, there is little evidence that environmental exposure to asbestos contributed to the deaths from respiratory cancer, mesothelioma and asbestosis in the Libby area.

#### The ATSDR Medical Testing Study

The ATSDR issued a report in August 2001 on the medical testing of individuals in the Libby area. The bulk of the report deals with the findings of a radiographic study on volunteers who had lived in the Libby area for at least six months prior to 1990. Thus, every subject in the study was either occupationally or environmentally exposed to asbestos prior to the closing of the mine in 1990.

Multivariate logistic regression analyses were conducted to examine the association of covariates such as age, gender, smoking habits, body mass index (BMI) and, most importantly, exposure to asbestos. A number of covariates were found to be significantly associated with radiographic abnormalities including age, gender, and smoking habits. With respect to asbestos exposure, activities that could have led to significant exposures were also found to be significantly associated with radiographic abnormalities. Thus the strongest risk factor for radiographic abnormalities was being a former WRG worker. 'Recreational' exposures to asbestos that could have resulted from activities such as vermiculite popping were also associated with radiographic changes.

Although the study suffers from such limitations as the self-selected study cohort, the statistical analysis appears to be appropriate. Overall, however, from this study it is impossible to assess the contribution that environmental exposure after 1990 made to the radiographic findings reported because one of the criteria for inclusion in the study was residence in Libby for at least 6 months prior to December 1990.

The radiographic studies conducted by Amandus et al (1987) and McDonald et al (1986) are relevant to this discussion. The results of these studies clearly indicate that, when radiographic end-points are considered, there is little evidence to suggest that Libby fibers are any more toxic than other asbestos fibers.

#### **X. The Whitehouse Study**

(Asbestos Related Pleural Disease due to Tremolite Causes Progressive Loss of Lung Function by A. C. Whitehouse)

EPA's June 4, 2002 response to Grace's comments on the Administrative Record states that, "...a study being prepared for publication by Dr. Alan Whitehouse found statistically significant progressive loss of lung function among 67 patients from Libby with only asbestos-related pleural abnormalities identified on either chest x-ray or CT scan."

EPA's comment is incorrect. What Dr. Whitehouse reported is that 67 of 123 patients who constituted the study population had no evidence of any interstitial disease identified on chest x-ray or high resolution CT scanning. Dr. Whitehouse purports to have found, as far as I could decipher from the Draft Report, a statistically significant annual loss of lung function, based on the average of the difference between initial and final pulmonary function measurements taken on 123 patients.

I can only surmise that the Whitehouse draft report represents the earliest stage of the "study being prepared for publication." The results reported are virtually uninterpretable, at least with respect to the principal question of interest, namely is decline in pulmonary function associated with asbestos exposure in a dose dependent way. I highlight some of the major deficiencies of the paper, which I strongly believe will have to be significantly revised before it is acceptable for publication in a respected peer-reviewed journal.

1. The analyses are inappropriate and do not exploit the fact that individual level longitudinal data are available. A better way to analyze these data would be to consider

each individual's response separately and address the correlations between consecutive readings by using standard statistical techniques. In particular the whole problem should have been set up as a regression problem in which pulmonary capacity is modeled as a function of time depending on a number of covariates such as age, sex, smoking history, obesity and most importantly history of exposure to asbestos. The coefficients of such a model could be estimated using generalized estimating equations (GEE) techniques.

2. Because Whitehouse uses averages, the decline in pulmonary function, which Whitehouse claims is statistically significant, could well be due to a few outliers in the data with the majority of individuals showing little or no decline in function except that attributable to aging.

3. Perhaps most importantly as has already been said above Whitehouse makes no attempt to correlate decline in pulmonary function with asbestos exposure in a quantitative fashion. Therefore he cannot conclude that the decline is related to exposure, much less to exposure received post 1990.


4. Whitehouse reports that he used a Sensormedics model 6200 to do the pulmonary function measurements before 1988 and a Medgraphics model 1085 since that time. His report does not give any indication of the number of patients whose initial and final measurements were made on different machines and whether any attempt was made to calibrate the machines to yield consistent results.

## **XI. Overall Conclusions**

A review of the literature dealing directly with the fibers found at Libby provides no evidence that these fibers are any more toxic than those that were considered in the development of the IRIS file. None of the studies can directly address the issue of whether exposures post-1990 and, in particular, current exposures at Libby pose a substantial danger to the community. EPA cites no evidence to support its contention that the population at Libby is sensitized due to prior exposure to asbestos and therefore

particularly susceptible to additional exposures. There is nothing in the literature to suggest that incremental exposures to asbestos act synergistically with previous exposures to create a risk that is greater than additive. The only way of assessing the risk posed by current environmental exposures at Libby is to conduct a sound quantitative risk assessment.

July 29, 2002

A handwritten signature in black ink, appearing to read "Suresh Moolgavkar". The signature is fluid and cursive, with the first name "Suresh" and last name "Moolgavkar" clearly distinguishable.

Suresh H. Moolgavkar, M.D., Ph.D.

## **XII..References**

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Moolgavkar SH, Turim J, Brown RC, Luebeck EG. 2001. Long man-made fibers and lung cancer risk. *Regulat Toxicol Pharmacol* **33: 138-146**.

## **CURRICULUM VITA**

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### Educational Background

M.B.B.S. (M.D.), Bombay University, 1965  
Ph.D., Mathematics, Johns Hopkins University, Baltimore, Maryland, 1973  
Postdoctoral Fellow, Departments of Pharmacology and Biophysics, Johns Hopkins Medical School, Baltimore, Maryland, 1966-68  
Senior Fellow, Department of Epidemiology, University of Washington, 1976-77

Medical Examinations:      ECFMG, FLEX

### Visiting Positions

Visiting Scientist, International Agency for Research on Cancer, Lyon, 11/79  
Visiting Scientist, Radiation Effects Research Foundation, Hiroshima, 4/81  
Visiting Scientist, Fred Hutchinson Cancer Research Center, Seattle, 8/15-12/15/82  
Visiting Professor, Department of Biostatistics, University of Washington, 8/15-12/15/82  
Visiting Scientist, German Cancer Research Center, Heidelberg, 6/15- 8/15/90

### Professional Appointments

Instructor in Mathematics, Johns Hopkins University, 1972-73  
Assistant Professor of Mathematics, Indiana University, Bloomington, 1973-77  
Associate, American Oncologic Hospital, Philadelphia, 1977-6/84  
Clinical Assistant Professor, Department of Research Medicine, University of Pennsylvania School of Medicine, 1977-6/80  
Member, Graduate Group in Epidemiology, University of Pennsylvania, 1977-6/84  
Epidemiologist, The Fox Chase Cancer Center, Philadelphia, 1977-6/84  
Research Physician, The Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, 7/79-6/84  
Adjunct Associate Professor, Department of Research Medicine, University of Pennsylvania School of Medicine, 7/80-6/84 .  
Adjunct Professor, Department of Biostatistics University of Washington, 7/84 - present

Professor, Department of Epidemiology, University of Washington, 7/84 - present  
Member, The Fred Hutchinson Cancer Research Center, Seattle, 7/84 - present

#### Awards and Honors

Faculty Research Fellowship of Indiana University, 1974-76  
Lester R. Ford Award of Mathematical Association of America, 1977  
Founders' Award, Chemical Industry Institute of Toxicology, 1990  
Member, American Epidemiological Society  
Distinguished Achievement Award, Society for Risk Analysis, 2001

#### Current Grant Support

"Risk assessment for complex mixtures", NIEHS, Co-Investigator, 10/1/98 - 9/30/02.  
"Biomathematical Approaches to Cancer", NIH/NCI, Principal Investigator, 9/30/97 - 9/29/02.  
"Biomathematical Approaches to Cancer and AIDS", NIH/NCI, Principal Investigator, 9/30/97-9/29/02.  
"Stochastic Models for Low-LET Radiation Risk Estimation at Low Dose and Dose-Rate", Principal Investigator, DOE, 9/1/99 - 8/30/02.

#### Publications

Mathematical (There is no seniority of authorship in mathematical papers.  
Authors appear in alphabetical order.)

1. On the existence of a universal germ of deformations for elliptic pseudo group structures on compact manifolds. Transactions of the American Mathematical Society 212:173-197, 1975.
2. On the signature of Fermat surfaces (joint with John Ewing), Michigan Math J 22:257-268, 1975.
3. Euler characteristics of complete intersections (joint with John Ewing), Proc Am Math Soc 56:390-391, 1976.
4. American mathematics from 1940 to the day before yesterday (joint with John Ewing, E. Gustafson, P. Halmos, W. Wheeler, and W. Ziemer), Am Math Monthly 83:503-516, 1976.
5. On a conjecture of Atiyah and Thom (joint with John Ewing), Preprint, Indiana University, 1976.
6. On the group of holomorphic line bundles on an algebraic surface (joint with John Ewing), Preprint, Indiana University, 1976.
7. Stable parallelizability of lens spaces (joint with John Ewing, Larry Smith, and R. E. Stong), J Pure and Applied Algebra 10:177-191, 1977.

#### Biomedical

8. Jarabak R, Colvin M, Moolgavkar S, Talalay P:  $\Delta^5$ -3-ketosteroid isomerase of *Pseudomonas testosteroni*. In "Methods in Enzymology" Vol. XV, RB Clayton editor, Academic Press, NY, 642-651, 1970.
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11. Moolgavkar S: The multistage theory of carcinogenesis and the age distribution of cancer in man. JNCI 61:49-52, 1978.
12. Moolgavkar S, Stevens RG, Lee JAH: The effect of age on the incidence of breast cancer in females. JNCI 62:493-501, 1979.
13. Moolgavkar SH, Venzon DJ: Two-event model for carcinogenesis: Incidence curves for childhood and adult tumors. Math Biosci 47:55-77, 1979.
14. Stevens RG, Moolgavkar SH: Estimation of relative risk from vital data: Smoking and cancers of the lung and bladder. JNCI 63:1351-1357, 1979.
15. Stevens RG, Lee JAH, Moolgavkar SH: No association between oral contraceptives and malignant melanoma. N Engl J Med 302:966, 1980.
16. Moolgavkar SH: The Neyman-Scott carcinogenesis model for low-dosage extrapolation. Math Biosci 50:155-156, 1980.
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19. Moolgavkar SH, Knudson AG: Mutation and cancer: A model for human carcinogenesis. JNCI 66:1037-1052, 1981.
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21. Stevens RG, Moolgavkar SH, Lee JAH: Temporal trends in breast cancer. Am J Epidemiol 115:759-777, 1982.
22. Moolgavkar SH: Risk assessment using vital data. In "Environmental Epidemiology: Risk Assessment." Proceedings of a SIMS Conference, RL Prentice and AS Whittemore, eds., SIAM, pp 175-192, 1982.
23. Moolgavkar SH: Model for human carcinogenesis: Action of environmental agents. Environ Health Perspect 50:285-291, 1983.
24. Moolgavkar SH: A model for human carcinogenesis: Hereditary cancers and premalignant lesions. Proceedings of the Seventh Chicago Cancer Symposium, "Cancer: Etiology and Prevention," RG Crispen, ed, Elsevier Science Publishing Co., Inc. pp. 71-77, 1983.
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26. Stevens RG, Moolgavkar SH: A cohort analysis of lung cancer and smoking in British males. Am J Epidemiol 119:624-641, 1984.
27. Stevens RG, Moolgavkar SH: Malignant melanoma: Dependence of site-specific risk on age. Am J Epidemiol 119:890-895, 1984.
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30. Moolgavkar SH, Lustbader ED, Venzon DJ: A geometric approach to non-linear regression diagnostics with application to matched case-control studies. Ann Statist 12:816-826, 1984.
31. Stevens RG, Moolgavkar SH: Smoking and cancer in Britain. Proceedings of the Fifth World Conference on Smoking and Health, 1984.
32. Moolgavkar SH: Some comments on the resources at RERF. In "Utilization and Analysis of Radiation Effects Research Foundation Data." Proceedings of a SIMS Conference, RL Prentice and DJ Thompson, eds., SIAM, pp. 274-279, 1984.
33. Lustbader ED, Moolgavkar SH, Venzon DJ: Tests of the null hypothesis in case-control studies. Biometrics 1017-1024, 1984.
34. Moolgavkar SH: Stochastic models for carcinogenesis. In: "Proceedings of the symposium on mathematics and computers in biomedical applications," J Eisenfeld and C DeLisi, editors, Alan Liss 325-331, 1985.
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41. Prentice RL, Moolgavkar SH, Farewell VT: Biostatistical issues and concepts in epidemiologic research. Journal of Chronic Diseases 38:1169-1183, 1986.
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43. Moolgavkar SH, Venzon DJ: Confidence regions in curved exponential families: Application to matched case-control and survival studies with general relative risk function. Annals of Statistics 15:346-359, 1987.
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50. Moolgavkar SH, Dewanji A: Biologically-based models for cancer risk assessment: A cautionary note. Risk Analysis, 8:5-6, 1988.
51. Moolgavkar SH, Dewanji A: Discussion of "From Mouse to Man: The Quantitative Assessment of Cancer Risks" by DA Freedman and H Zeisel. Statistical Science, 3:39-41, 1988.
52. Moolgavkar SH, Dewanji A, Venzon DJ: A Stochastic two-stage model for cancer risk assessment I: The hazard function and the probability of tumor. Risk Analysis, 8:383-392, 1988.
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65. Moolgavkar SH, Luebeck G, DeGunst M: Two mutation model for carcinogenesis: Relative roles of somatic mutations and cell proliferation in determining risk. In Scientific Issues in Quantitative Cancer Risk Assessment, SH Moolgavkar (ed.), Birkhauser Boston, 1990, 136-152.

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81. Moolgavkar SH, Luebeck EG, Krewski D, Zielinski JM: Radon, cigarette smoke, and lung cancer: A reanalysis of the Colorado Plateau miners' data. Epidemiology, 4: 204-217, 1993.

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83. Zheng CJ, Byers B, Moolgavkar SH: Allelic instability in mitosis: A unified model for dominant disorders. Proc. Natl. Acad. Sci. USA, 90: 10178-10182, 1993.
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85. Moolgavkar SH, Luebeck EG: Incorporating cell proliferation kinetics into models for cancer risk assessment, Toxicology, 102: 141-147, 1995.
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88. Moolgavkar SH: Air pollution and mortality (letter) N. Eng J Med, 330: 1237-1238, 1994.
89. Moolgavkar SH: Biological models of carcinogenesis and quantitative cancer risk assessment. Guest Editorial. Risk Analysis, 14: 879-882, 1994.
90. Moolgavkar SH, Luebeck EG, Hall TA, Anderson EL: Particulate air pollution, sulfur dioxide, and daily mortality: A reanalysis of the Steubenville data. Inhalation Toxicology, 7: 35-44, 1995.
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92. Luebeck EG, Grasl-Kraupp B, Timmermann-Trosiener I, Bursch W, Schulte-Hermann R, Moolgavkar SH: Growth kinetics of enzyme altered liver foci in rats treated with phenobarbital or  $\alpha$ -hexachlorocyclohexane. Toxicology and Applied Pharmacology, 130: 304-315, 1995.
93. EG Luebeck, SH Moolgavkar: Biologically based cancer modeling. In 'Toxicology and Risk Assessment', edited by AM Fan and LW Chang; Marcel Dekker, Inc., New York, 1995, pp 533-555.
94. Moolgavkar SH: When and how to combine results from multiple epidemiological studies in risk assessment. "The Proper Role of Epidemiology in Regulatory Risk Assessment", editor: John Graham, Elsevier, New York, 1995, 77-90.
95. Moolgavkar SH, Luebeck EG, Hall TA, Anderson EL: Air pollution and daily mortality in Philadelphia. Epidemiology, 6: 476-484, 1995.
96. Luebeck EG, Curtis SB, Cross FT, Moolgavkar SH: Two-stage model of radon-induced malignant lung tumors in rats: effects of cell killing. Radiation Research, 145: 163-173, 1996.
97. Moolgavkar SH, Luebeck EG, Buchmann A, Bock KW: Quantitative analysis of enzyme-altered foci in rats initiated with diethylnitrosamine and promoted with 2,3,7,8-tetrachlorodibenzo-p-dioxin or 1,2,3,4,6,7,8-heptachloro-p-dioxin. Toxicology and Applied Pharmacology, 138: 31-42, 1996.

98. Moolgavkar SH, Luebeck EG, Hall TA, Anderson EL: Particulate air pollution and mortality. Letter to the Editor, Epidemiology, 7: 212-213, 1996.
99. Moolgavkar SH, Luebeck EG: A critical review of the evidence on particulate air pollution and mortality, Epidemiology, 7: 420-428, 1996.
100. Leroux BG, Lesenring WM, Moolgavkar SH, Faustman EM: A biologically based dose-response model for developmental toxicology, Risk Analysis, 16: 449-458, 1996.
101. Dewanji A, Luebeck EG, Moolgavkar SH: A biologically-based model for the analysis of premalignant foci of arbitrary shape. Mathematical Biosciences, 135: 55-68, 1996.
102. Moolgavkar SH, Luebeck EG, Anderson, EL: Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology, 8(4): 364-370, 1997.
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104. Kai M, Luebeck EG, Moolgavkar SH: Analysis of solid cancer incidence among atomic bomb survivors using a two-stage model of carcinogenesis. Radiation Research, 148: 348-358, 1997.
105. Moolgavkar SH, Lee JAH, Stevens RG: Analysis of vital statistical data. In "Modern Epidemiology", 2<sup>nd</sup> edition K. Rothman and S. Greenland, editors, Lippincott-Raven, Philadelphia, 1998.
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  120. Moolgavkar SH, Luebeck EG, Turim J, Brown RC. Lung cancer risk associated with exposure to man-made fibers. Drug and Chemical Toxicology, 23:223-242, 2000.
  121. Moolgavkar SH, Hazelton WF, Luebeck EG, Levy D, Sheppard L. Air pollution, pollens, and admissions for chronic respiratory disease in King County. Inhalation Toxicology, 12(Supplement 1):157-171, 2000.
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135. Moolgavkar SH. Air pollution and daily mortality in two US counties: Season-specific analyses and exposure-response relationships. Inhalation Toxicology, in press.
136. Luebeck EG, Moolgavkar SH. Multistage carcinogenesis and the incidence of colorectal cancer. Proc. Natl Acad. Sci USA, in press.

### Books

1. Modern Statistical Methods in Chronic Disease Epidemiology. SH Moolgavkar and RL Prentice, Editors, John Wiley, 1986.
2. Tobacco Smoking, IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Volume 38, IARC, Lyon, 1986 (member of the working group).
3. Scientific Issues in Quantitative Cancer Risk Assessment. SH Moolgavkar, Editor, Birkhauser Boston, 1990.
4. Quantitative Estimation and Prediction of Human Cancer Risk. SH Moolgavkar, D Krewski, L Zeise, E Cardis and H Moller, Editors, IARC Scientific Publications 131, 1999.

### Selected Professional Activities

- Editorial Board of "Genetic Epidemiology", 1984-88
- Member, IARC (International Agency for Research on Cancer) working group on Tobacco Smoking
- Session Chairman at International Symposium: "Time Related Factors in Cancer Epidemiology", held at NIH in April 1985

- Co-chairman of SIMS conference "Modern Statistical Methods in Chronic Disease Epidemiology" held in Alta, Utah in June 1985
- Member, NIH Special Study Section for Biometry
- Member, NSF panel to review Scientific bases of risk assessment methodologies
- Member, Advisory Committee to review risk assessment program of Armstrong Laboratories, Wright-Patterson Air Force Base, 1987
- Member, External Scientific Committee to review the program of the Radiation Epidemiology Branch, NCI, 1987
- Consultant, Fox Chase Cancer Center
- Consultant, University of Nebraska Medical Center
- Consultant, Health and Welfare, Canada
- Organizer and Chair, SIMS conference "Scientific Issues in Quantitative Cancer Risk Assessment", held in Snowbird, Utah, June 1989
- Member, Scientific Advisory Panel to review Risk Assessment program of the National Center for Toxicologic Research, 1992.
- Member, Scientific Advisory Panel to review the EPA Dioxin Health Assessment document, 1992.
- Member, Scientific Advisory Panel to the Chemical Industry Institute of Toxicology, 1992 - present.
- Member, Working Group on quantitative estimation and prediction of cancer risk, IARC, Lyon, 1993.
- Senior Editor of monograph 'Quantitative Estimation and Prediction of Cancer Risk' IARC Scientific Publications, No. 131, 1999.
- Member, Health Effects Institute Expert Panel for re-analyses of critical air pollution studies, 1997 – present.
- Co-chairman, International Conference on Mathematical Models in Cancer, Park City, Utah, 1998.
- Area Editor for Health and Environment, *Risk Analysis – An International Journal*. Jan 2000 - .

#### Selected Invited Talks

- International Symposium, "Time Related Factors in Cancer Epidemiology", NIH, April, 1985
- SIMS conference, "Modern Statistical Methods in Chronic Disease Epidemiology", Alta, Utah, June 1985
- Seminar, "Stochastic Models for Carcinogenesis and Risk Assessment", EPA, Washington, DC, 1985.
- Seminar, "General Relative Risk Models for Case-Control Studies", Johns Hopkins University, School of Public Health, Baltimore, MD, 1985.
- Seminar, "Two-Stage Model for Carcinogenesis and the IPI Protocol", Battelle PNL, Richland, WA, 1986.
- School of Public Health grand rounds, "A Cohort Analysis of Smoking and Cancers of the Lung, Bladder and Pancreas", Department of Biostatistics Seminar "General

- Relative Risk Regression Models for Epidemiologic Studies", University of Pittsburgh, Pittsburgh, January 1987
- Symposium on Quantitative Assessment of Cancer Risk, "Two-Stage Model for Carcinogenesis: Implications for Risk Assessment", Washington, DC, February 1987
  - Risk Assessment Workshop, "Biologically-Based Carcinogenesis Models for Risk Assessment", Washington, DC, March 1987
  - American Statistical Association Annual Meeting, "Origin Invariant Relative Risk Functions", "Multi-Stage Models for Cancer Risk Assessment", San Francisco, August 1987
  - EPA Toxicology and Microbiology Seminar Series, "Two Mutation Model for Cancer Risk Assessment", Cincinnati, October 1987
  - 17th Conference on Toxicology, "Biologically Motivated Two-Stage Model for Carcinogenesis", Wright-Patterson Air Force Base, Dayton, November 1987
  - University of Wisconsin Seminars, "Two-Stage Model for Carcinogenesis", Department of Human Oncology, "Curvature and Inference in Exponential Families: Application to Relative Risk Regression Models", Department of Statistics, Madison, November 1987
  - Fox Chase Cancer Center Seminar, "Cox Regression for the Innocent Bystander", Philadelphia, December, 1987
  - Biopharmaceutical Section of ASA, gave a tutorial and short course on "Modern Statistical methods in Chronic Disease Epidemiology" in conjunction with Ross Prentice (five lectures each), Newark, December 1987
  - Risk Assessment Workshop, "Biologically-Based Carcinogenesis Models for Risk Assessment", Washington, DC, March 1988
  - Health and Welfare Canada, "Biologically-Based Carcinogenesis Models for Risk Assessment", Ottawa, March 1988
  - Carleton University, "Curvature and Inference in Exponential Families: Application to Relative Risk Regression Models", Ottawa, March 1988
  - University of Nebraska Medical Center, "A Two-Stage Model for Carcinogenesis and its Implications for Risk Assessment", May 1988
  - NATO Workshop on Biologically-Based Methods for Cancer Risk Assessment, "Cancer Models and Risk Assessment", Corfu, Greece, June 1988
  - Radiation Research Society, Annual Meeting, Seattle, WA, 1989
  - SIMS Conference, Alta, Utah, 1989
  - McArdle Laboratory, University of Wisconsin, Madison, 1989
  - Society for Risk Analysis, Annual Meeting, San Francisco, CA, 1989
  - International Conference, "Chemically Induced Cell Proliferation: Implications for Risk Assessment", Austin, Texas, 1989
  - Invited Participant, Workshop on Risk Assessment for Benzene, Georgetown University, 1989
  - University of Cincinnati, Environmental Health Center, 1990
  - University of Pittsburgh, Department of Biostatistics, 1990
  - University of Illinois, Center for Environmental Studies, 1990
  - German Cancer Research Center, Heidelberg, Germany, 1990
  - University of Tübingen, Tübingen, 1990

- University of Vienna Cancer Center, Vienna, Austria, 1990
- BASF, Toxicology group, Mannheim, 1990
- International Cancer Congress, Hamburg, 1990
- National Academy of Sciences, Committee on Risk Assessment Methodology, Washington, DC, 1990
- Hanford Symposium on Health and the Environment, Battelle PNL, Richland, 1990
- Joint U.S., Japan Cancer Meeting, Hawaii, 1991
- International Workshop "Biophysical Modelling of Radiation Carcinogenesis", Padua, Italy, 1991
- NATO Workshop on Risk Assessment, Athens, Greece, 1991
- Princess Takamatsu Cancer Congress, Tokyo, Japan, 1991
- International conference on Cell Proliferation in Carcinogenesis, NIEHS, North Carolina, 1992
- International Toxicology Conference, Rome, Italy, 1992
- Workshop on Risk Assessment and Low Dose Extrapolation, Zurich, Switzerland, 1992
- International Workshop on Mouse Liver Tumors, Washington D.C., 1992
- European Toxicology Meeting, Mainz, Germany, 1993
- International Symposium on Quantitative Risk Assessment, Research Triangle Park, NC, 1993
- AACR International Workshop on Risk Assessment, Whistler BC, 1994.
- Society for Risk Analysis sessions on cancer risk assessment and on air pollution, Honolulu, 1995.
- HEI workshop on Diesel Exhaust, San Francisco, 1996.
- Berkeley symposium on Benzene and Leukemia, Napa Valley, 1996.
- International symposium on low-dose and low-dose-rate radiation, Stratford-on-Avon, UK, 1997 (invited keynote speaker).
- International symposium on Health Effects of Particulate Air Pollution, Prague, 1997 (invited speaker).
- International symposium on Statistics in the Environment, Enschede, The Netherlands, 1997 (invited speaker).
- Seminar speaker, Netherlands Institute for Health and the Environment, 1997.
- International meeting of the Bernoulli Society, Calcutta, India, 1997 (invited speaker).
- Sixth European Meeting on Hepatocarcinogenesis, Vienna, September 1999, invited speaker.
- International Workshop on Mathematical Models in Radiation Carcinogenesis, Kyoto, March, 2001, invited speaker.
- International Biometrics Conference, Homburg, Germany, March 2001, invited speaker.